Chapter 6

Domesticating Poliovirus: Laboratory Monkeys and Vaccine Production

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VACCINES ARE A TECHNOLOGY—a form of artifice—that reproduce the biological consequences of a first, authentic historical encounter between an individual and a virus, or a community and a virus by means of large-scale vaccination campaigns.[1] The artifice of vaccination depends entirely on the manipulation of nature. Vaccines are, after all, made from pathogens themselves. In anti-vaccination writings, authors focus on the unnatural additives to vaccines: the mercury (thimerosal) used as a preservative, the formaldehyde used to inactivate viruses and toxins, and the aluminum that is used as an adjuvant.[2] Yet the use of the viruses themselves is just as remarkable. The process of polio vaccine production, for example, is a process of domestication as much as a process of fabrication. Within the landscapes of laboratories and across the topographies of animal bodies, wild polioviruses are taken and transformed into viruses under human control, which can then be deployed in large-scale vaccination programs. Sometimes, new viruses literally evolve out of the research process leading up to vaccine production, as with a neural-adapted, virulent strain of polio called the MV strain affecting only the central nervous system and no longer replicating in the intestines.[3] In a 1974 interview with Saul Benison, Albert Sabin spoke with some regret about early work he had done using the MV strain, rather than "strains as they are found in nature, before they have been changed by many passages in the laboratory." He referred to

Figure 1. Preparation of measles vaccine at the Tirana Institute of Hygiene and Epidemiology, Tirana, Albania, c.1969–1979. WHO / D. Henrioud (Photographer).

strains including MV and others transformed in the laboratory as "artifacts" that were used out of ease, but did not permit conclusions about the "human disease or the original virus."[4]

Other-than-human nature is subjugated in many different ways in vaccine research and production. To grow viruses needed for vaccines outside of the human body historically required other bodies. The classic example of their deployment was Edward Jenner's use of pus from cowpox blisters (albeit found on the hands of milkmaids, but contracted originally from cows) to inoculate against smallpox. Fertilized chicken eggs are used to grow vaccine strains of influenza, and historically limited supplies of fertilized chicken eggs impeded rapid vaccine production.[5]

In the case of polio, monkeys were essential to biomedical research. Unlike most other laboratory animals (rabbits, guinea pigs, and mice), they were susceptible to polioviruses and were therefore essential for laboratory

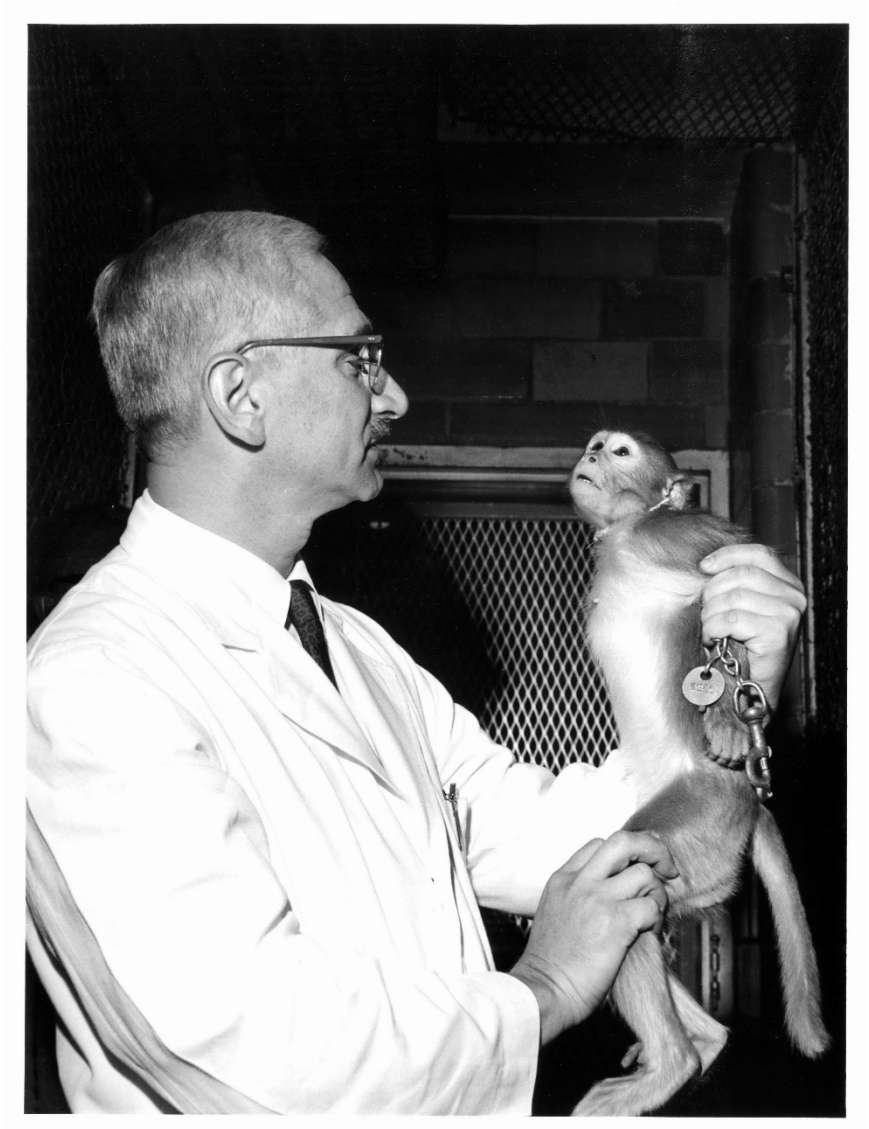

Figure 2. Albert Sabin and a research monkey, c.1950s. Courtesy the Hauck Center for the Albert B. Sabin Archives, Henry R. Winkler Center for the History of the Health Professions, University of Cincinnati Libraries.

research on the disease. Indeed, they shaped the conditions of research into polio from 1908 until 1939. This included the need to transport monkeys during polio epidemics, as when seventy-five travelled by train with researchers to Los Angeles to investigate an outbreak there in 1934.[6] By 1939, a mouse-adapted strain (the Lansing strain) of polio had been isolated that permitted some experimental effort to be diverted from monkey to mouse bodies.

Research undertaken between 1948 and 1955 at first promised to free monkeys entirely from their role in poliovirus research, but ended up greatly amplifying demand for their bodies. Researchers had attempted to grow poliovirus in vitro, "artificially" or "outside of the body," with varying degrees of success since the 1910s.[7] Then, in a 1949 article published in *Science*, John Enders, Thomas Weller, and Frederick Robbins described cultivating the Lansing strain in tissue cultures made from human embryos, including non-nervous tissues. This research demonstrated conclusively that polio was not exclusively a disease of the central nervous system.[8] More importantly, this work, by enabling virus reproduction in tissue cultures—a preparation made from living tissue to serve as an artificial medium for cell growth—liberated polioviruses from bodies, whether monkey, mouse, or human. This was a precursor to the mass reproduction of domesticated poliovirus strains needed for large-scale vaccine trials.

The creation of ambiguous boundaries between nature and laboratory-based artifice was central to the domestication of polioviruses, as seen with the evolution of laboratory-born poliovirus strains. The development of tissue cultures in turn moved much of the work from monkey bodies into test tubes and Povitsky bottles. But tissue cultures also needed to be kept and fed in conditions that closely approximated those experienced by living bodies. Techniques used by Jonas Salk and colleagues in his Pittsburgh

Figure 3. Dr. Leone Farrell and the "Toronto method" of poliovirus cultivation, Connaught Laboratories, 1953–1954. Sanofi Pasteur Canada (Connaught Campus) Archives, Toronto.

laboratory drew on a method developed by George Otto Gey, which kept the tissue culture in motion, rocking it back and forth like a sleeping baby, exposing it alternately to air and food.[9] The human embryonic tissues used by Enders, Weller, and Robbins were expensive and difficult to procure, however. By 1951, Salk and his colleagues had refined a technique to produce tissue cultures from monkey kidney cells for propagating large volumes of poliovirus. Salk and his colleagues used a nutrient solution called Medium 199, synthesized at the University of Toronto's Connaught Laboratories. It contained over sixty ingredients ranging from vitamins to table salt, and included experimental amino acids, cell surface agents, nucleic acids, growth factors, and iron. The medium kept the tissue culture cells alive long enough to be infected by the virus, which was then allowed

to multiply until the cells were completely destroyed, leaving only the poliovirus suspended in a solution of Medium 199.[10]

John R. Paul, medical historian and polio researcher, had reflected that with Enders, Wellers, and Robbins' work, it was "wonderful to say, … that at long last monkeys, which had been so essential in the poliomyelitis laboratory, could be replaced by tissue cultures, for certain purposes at least. This marked an end, at least partially, of the monkey era."[11] Partially is the operative word here. Monkeys continued to be used in laboratories, even if research no longer depended on them. More important, the tissue cultures that replaced living animals had to be manufactured from monkey bodies. Really, then, this simply marked a shift from dealing with whole monkeys to monkey parts. Indeed, the scale of monkey harvesting increased dramatically in the context of vaccine production. Thus the 1949 article by Enders, Weller, and Robbins can be seen as changing experimental conditions for virology in general by leading to "the large-scale employment of nonhuman primates in the virus laboratory," as well as paving the way for the manufacture of a polio vaccine.[12]

In 1953, the National Foundation for Infantile Paralysis requested that the Connaught Medical Research Laboratories in Toronto assist in the preparation of virus fluids (infected tissue cultures) needed for the American trials of Salk's vaccine. Scientists at Connaught had first engaged in poliomyelitis research in the late 1930s. Researchers were based either at the University of Toronto campus in downtown Toronto, Ontario, or out at what was initially called "the Farm"—a fifty-eight-acre property on the northern outskirts of the city. Both were essential landscapes of medical science in Canada, as Joanna Dean has also described in her chapter in this volume. The Farm was renamed the Dufferin Division after Princess Alice, Countess of Athlone, visited in 1943 and commented that the work was not what she expected of a "farm."[13]

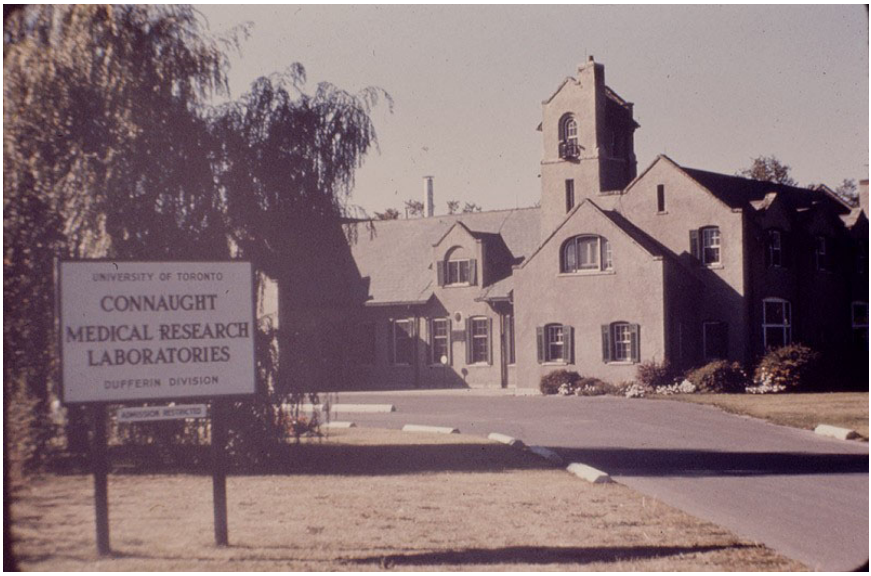

Figure 4. Dufferin Division of the Connaught Medical Research Laboratories (after the name change), 1940s. Sanofi Pasteur Canada (Connaught Campus) Archives, Toronto.

At the Farm, horses were kept for the preparation of diphtheria antitoxin, which required injecting and bleeding the horses as well as facilities for refining and concentrating the antitoxin. Calves were kept for the manufacture of smallpox vaccine, and cows for the manufacture and testing of "beef" liver extracts, used in the regeneration of hemoglobin. Insulin was prepared from an alcoholic extract of minced pancreas glands of cattle or hogs. Cows were also used for research into bovine tuberculosis. The Farm housed colonies of guinea pigs, white mice, and rats. Its buildings featured animal operating theatres, laboratories, housing for staff and researchers, and some veterinary research facilities.[14] Other manufacturing facilities and laboratories were located downtown in the University of Toronto's Department of Hygiene, including cages for monkeys.[15] By the 1950s, when poliomyelitis vaccine development was at its peak, the monkeys too were moved out to the Farm.

In 1953, workers and scientists at Connaught prepared 5,521 litres of virus fluids that year, using over 7,000 monkeys in their production.[16] In 1954, the stables at the Dufferin Division were renovated to accommodate monthly shipments that had grown to as many as 1,500 monkeys. This enormous increase in demand for monkeys came not only from the Connaught Laboratories themselves, but also from laboratories across North America that were racing to develop an effective vaccine at the height of polio epidemics. Rhesus macaques were the animal of choice because their kidneys could be used for tissue cultures and because they were relatively easy to procure from dealers in India. Then, in 1955, concerned about these animals' deaths and the poor conditions they encountered in transport, India imposed an export embargo on macaques.[17] The importance of these monkeys to polio vaccine development led to political pressure from the United States and the United Kingdom. Both countries pushed India to reopen the trade on the condition that the monkeys be treated humanely and be used exclusively for medical research and vaccine production.[18] In the context of societal anxiety over polio, Neel Ahuja has argued "that national officials [in the US] in charge of marshalling 'research resources' established the rhesus as the primary biomedical model for the human to be imported and preserved as a vital national resource."[19]

Even as rhesus macaques were becoming a biomedical model for humans, they were animals in their own right, needing care and treatment. Through the 1970s some continued to express concern that appropriate conservation measures were not being observed in the capture of macaques and other species earmarked for research purposes at the National Institutes of Health, and at private pharmaceutical research labs like the Connaught. There was also concern about the hazards posed by monkey bodies. In a 1971 review of the role of primates in virology, S.S. Kalter and

R.L. Heberling emphasized that "monkeys and apes must not be considered simply as 'test tubes'… but as biological entities harboring a multitude of microbial and parasitic forms."[20] Certain microbes and parasites were encouraged by the trade and commerce in monkeys for experimentation. Tom Rivers, a leading American virologist at the Rockefeller Institute, described how

> [m]any investigators, in order to cut costs, would sell their monkeys to dealers if they survived given experiments and appeared hale and hearty. The dealers, in turn, would resell the monkeys to other laboratories. Under such conditions, an investigator could buy a monkey from a dealer and have no reason to suspect that the animal had ever seen a poliovirus when, in fact, it may have had all three types of poliovirus. And how was one to know at that time which type or combination of types it had had? No one knew about types. You can imagine how cockeyed some of the experimental results were, and they were cockeyed![21]

Kalter and Heberling emphasized that practices for the capture, shipping, and handling of non-human primates encouraged the spread of viruses between monkeys, and even across different monkey species. They noted that even when animals were trapped individually, they were then kept until shipment in gang cages, where viruses could readily be transmitted between animals. Likewise, cages that were not cleaned properly between shipments could harbour viruses and bacteria that could infect more recently trapped animals. Conditions in the exporting and importing countries were, these authors noted, "generally unhygienic," with little attempt made to observe public health or sanitary practices. "Frequently," they wrote, "the problem of organism interchange is

compounded in the importers' holding areas as different species from all over the world are now brought together."[22]

Beyond the "cockeyed" research results Rivers described, the use of monkey kidneys for tissue culture, when combined with researchers' inattention to the monkeys as disease carriers in their own right, had serious implications in the development of the polio vaccine. Monkey bodies were far from sterile test tubes, and over time, researchers became more aware of the dangers posed by indigenous monkey viruses. In 1932, William Brebner, a bacteriologist at the Rockefeller Institute working on poliomyelitis and a colleague of Albert Sabin, was infected and died after being bitten by a macaque. The virus he succumbed to was later identified as Herpes B (for Brebner), and the infectious agent became generally known as "virus B."[23] Given that this virus had been discovered in the process of poliomyelitis research, those involved in the development of vaccines using monkey kidney tissues recognized the possible presence of the virus in vaccines. They conducted significant testing, therefore, to ensure that the "virus was inactivated more quickly by the amount of formaldehyde used in preparing the vaccine than polioviruses and that no danger existed."[24] But virus B was by no means unique. As Kalter and Heberling described almost twenty years later, there were numerous potential viruses that existed in monkeys at the point of capture, or which could be transmitted under the conditions in which they were transported. Some of these viruses would go on to infect the tissue cultures, with visible effect: researchers had to dispose of waste tissue cultures and vaccines as part of the manufacturing process. One virus, later called Simian virus 40 (SV40), did not cause sickness in infected macaques, but has since been linked to the development of mesothelioma, osteosarcoma, and ependymoma cancers in humans. Polio vaccines produced between 1955

and 1963 are thought to have been widely contaminated with SV40, due to the use of infected monkey kidney tissues.[25]

Studying the process of vaccine discovery and production involves tracing the experiences of polioviruses into laboratories. In these landscapes of science, we see the domestication of polioviruses and the evolution of new poliovirus strains as a result of laboratory research conditions. We also see the role of monkeys in enabling the domestication of such viruses, and latterly, the liberation of domesticated polioviruses from the topographies of human and other-than-human bodies through the development of tissue cultures. This liberation led to an intensified dependence on monkeys as source material for substrate, rather than as living organisms. This narrowed focus on partial, rather than whole monkeys made possible the development of a vaccine that was fundamental to human control of wild polioviruses.

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[1] The name "vaccine" comes from the Latin term for "cow" (*vacca*), since the first vaccine was made from fluid from a cowpox pustule on a milkmaid's wrist. This infectious matter was inoculated into a boy, who thereafter had immunity to smallpox. Although the boy had not previously encountered the relevant pathogen, the vaccine had reproduced or mimicked such an encounter within the boy's body, yielding the biological reaction needed to confer immunity. Modern vaccination programs multiply such encounters to encompass entire communities.

Thanks to Chris Sellers for this insight into vaccines as a technology.

[2] Adjuvants are substances added to a vaccine to enhance the body's immune response. For an example of such anti-vaccination writing, see Janine Roberts, "Polio: the Virus and the Vaccine," special report in *The Ecologist* 34, no. 4 (2004): 35–52.

[3] Naomi Rogers, *Dirt and Disease: Polio before FDR* (New Brunswick, NJ: Rutgers University Press, 1996), 24.

[4] Transcript of interview of Albert B. Sabin conducted by Saul Benison, March 2, 1974, tape 2, pp. 57–58, Albert B. Sabin Archives, Henry R. Winkler Center for the History of the Health Professions, University of Cincinnati Libraries, http://hdl.handle.net/2374.UC/701637.

[5] George Dehner, *Influenza: A Century of Science and Public Health Response* (Pittsburgh: University of Pittsburgh Press, 2012), 63, 166.

[6] Gareth Williams, *Paralysed with Fear: The Story of Polio* (Basingstoke: Palgrave Macmillan, 2013), 103, https://doi.org/10.1057/9781137299765.

[7] John R. Paul, *A History of Poliomyelitis* (New Haven and London: Yale University Press, 1971), 372; A.B. Sabin and P.K. Olitsky, "Cultivation of Poliovirus *in vitro* in Human Embryonic Nervous Tissue," *Proceedings of the Society for Experimental Biology and Medicine* 34, no. 3 (1936): 357, https://doi.org/10.3181/00379727-34-8619c.

[8] This work also led to Enders, Weller, and Robbins sharing the 1954 Nobel Prize in Physiology or Medicine. See http://www.nobelprize.org/nobel_prizes/medicine/laureates/1954/.

[9] For the role of Gey and HeLa cells in polio research, see Rebecca Skloot, *The Immortal Life of Henrietta Lacks* (New York: Crown Publishers, 2010), 93–97.

[10] Christopher James Rutty, "'Do Something!… Do Anything!': Poliomyelitis in Canada 1927–1962" (PhD diss., University of Toronto, 1995), chap. 7.

[11] Paul, *History*, 374.

[12] S.S. Kalter and R.L. Heberling, "Comparative Virology of Primates," *Bacteriological Reviews* 35, no. 3 (1971): 311, https://doi.org/10.1007/978-1-4615-8990-7_6.

[13] Robert D. Defries, *The First Forty Years, 1914-1955, Connaught Medical Research Laboratories, University of Toronto* (Toronto: University of Toronto Press, 1968), 209.

[14] Ibid., 28–29, 41–42, 96, 314–17.

[15] P.A. Bator and A.J. Rhodes, *Within Reach of Everyone: A History of the University of Toronto School of Hygiene and the Connaught Laboratories*, vol. 1 (Ottawa: Canadian Public Health Association, 1990), 176.

[16] Defries, *Forty*, 273.

[17] For more details, see Deborah Rudacille, *The Scalpel and the Butterfly: The Conflict between Animal Research and Animal Protection* (Berkeley and Los Angeles: University of California Press, 2000), chap. 5; and Andrew N. Rowan, *Of Mice, Models, and Men: A Critical Evaluation of Animal Research* (Albany: State University of New York Press, 1984), 115.

[18] Rowan, *Mice*, 115. See also UK Hansard HC Deb 25 April 1955, vol. 540, cc620-4, http://hansard.millbanksystems.com/commons/1955/apr/25/poliomyelitis-vaccine-1.

[19] Neel Ahuja, "Macaques and Biomedicine: Notes on Decolonization, Polio, and Changing Representations of Indian Rhesus in the United States, 1930–1960," in *The Macaque Connection: Cooperation and Conflict between Humans and Macaques*, ed. Sindhu Radhakrishna, Michael A. Huffman, and Anindya Sinha (New York: Springer, 2013), 72, https://doi.org/10.1007/978-1-4614-3967-7_5.

[20] Kalter and Heberling, "Virology," 311.

[21] Saul Benison, ed., *Tom Rivers: Reflections on a Life in Medicine and Science* (Cambridge: MIT Press, 1967), 255.

[22] Kalter and Heberling, "Virology," 314–15.

[23] Jason D. Pimentel, "Herpes B virus – 'B' is for Brebner: Dr. William Bartlet Brebner (1903–1932)," *Canadian Medical Association Journal* 178, no. 6 (2008): 734, https://doi.org/10.1503/cmaj.071098.

[24] Defries, *Forty*, 279.

[25] For more on monkey viruses and vaccine production, see Keerti V. Shah, "Simian Virus 40 and Human Disease," *Journal of Infectious Diseases* 190, no. 12 (2004): 2061–64; and Debbie Bookchin and Jim Schumacher, *The Virus and the Vaccine: The True Story of a Cancer-Causing Monkey Virus, Contaminated Polio Vaccine, and the Millions of Americans Exposed* (New York: St. Martin's Press, 2004). See also the Public Health Agency of Canada's webpage on Polio Vaccine and SV40: http://www.phac-aspc.gc.ca/im/polio-eng.php.